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PATENT SPECIFICATION

Inventor: LEE H. MACDONALD

810,537

Date of Application and filing Complete Specification: Sept. 4, 1957.

No. 27938/57.

Complete Specification Published: March 18, 1959.

Index at acceptance:—Classes 81(1), B2(E:F:G:H:L:M:N:R:S); and 127, G.

International Classification:—A23l. A61k.

COMPLETE SPECIFICATION

Sweetening Composition

We THE UPJOHN COMPANY

SPECIFICATION NO. 810,537

INVENTOR:- LEE H. MACDONALD

By a direction given under Section 17(1) of the Patents Act 1949 this application proceeded in the name of The Upjohn Company, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America.

THE PATENT OFFICE,
5th March, 1959

DB 10089/1(33)/3739 150 2/59 R

similar to the other sensory mechanisms of the human body. The sensory mechanism consists of a peripheral end-organ or receptor, the pathway along which sensory stimuli are transmitted, and a centre in the cerebral cortex which analyzes and interprets the sensation. Taste buds in man are generally confined to the oral cavity, the tongue having by far the greatest number. Several other factors enter into the flavour of a substance, such as olfactory, tactual, thermal and physical-chemical considerations.

Generally, however, flavours may be classified as salty, sweet, bitter and sour. These are the "tastes" which are discernible by the taste buds of the oral cavity in man. There are, of course, various modifications and intensities of these flavours.

Some of these flavours are regarded as favourable, others are not. The intensity of these flavours is an important factor. Sweet is generally regarded as pleasant while bitter is seldom regarded as pleasant. The intensity of a bitter taste has a greater impact on most people than salty and sour.

[*Price 3s. 6d.*]

position comprising essentially of three to ten parts by weight of saccharin or its alkali metal salts to each part by weight of cyclamate sodium and/or cyclamate calcium, wherein saccharin is present in an amount not less than one per cent by weight. In its preferred embodiment the present invention comprises an oral fluid, pharmaceutical composition comprising a bitter tasting drug, from three to ten parts by weight of saccharin or its alkali metal salts to each part by weight of cylamate sodium or cyclamate calcium, wherein the saccharin is present in an amount not less than one percent by weight.

Although it has been common practice to utilize sucrose and other sweetening agents to modify the taste of bitter drugs, it has been believed impossible prior to the present invention to utilize sufficient amounts of these materials to neutralize the bitter taste of many of the best-known and most effective drugs. Although it has long been recognized that artificial sweetening agents such as saccharin are many times as sweet as sucrose, it was thought that, in high concentrations, saccharin

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COMPLETE SPECIFICATION

Sweetening Composition

We THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Michigan, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a sweetening composition and more particularly to compositions comprising saccharin suitable for use in oral fluid pharmaceutical preparations, or in tablet form.

Flavour can be defined as that quality of anything which affects the taste. The volatility of a substance has some bearing on its taste; in fact, without the sense of smell the true taste of many substances would be entirely lost or so altered as to be misleading. Generally speaking the organs of taste and smell are similar to the other sensory mechanisms of the human body. The sensory mechanism consists of a peripheral end-organ or receptor, the pathway along which sensory stimuli are transmitted, and a centre in the cerebral cortex which analyzes and interprets the sensation. Taste buds in man are generally confined to the oral cavity, the tongue having by far the greatest number. Several other factors enter into the flavour of a substance, such as olfactory, tactual, thermal and physical-chemical considerations.

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Nonnutritive sweetening agents are used extensively by many industries, especially for individuals under dietary restrictions. Among others, the food industry, the beverage industry and the pharmaceutical industry utilize substantial amounts of such sweeteners. In the pharmaceutical industry it has been a considerable problem to neutralize the bitter flavour of many therapeutically active materials. This is an especially important problem in pediatric formulas which must ordinarily be administered in fluid form.

It is therefore an object of the present invention to provide sweetening agents which can be utilized wherever a high degree of sweetening power is required, especially to improve the flavour of oral fluid preparations of bitter drugs. Other objects will be apparent to one skilled in the art to which this invention pertains.

The foregoing and additional objects have been accomplished by the provision of a composition comprising essentially of three to ten parts by weight of saccharin or its alkali metal salts to each part by weight of cyclamate sodium and/or cyclamate calcium, wherein saccharin is present in an amount not less than one per cent by weight. In its preferred embodiment the present invention comprises an oral fluid, pharmaceutical composition comprising a bitter tasting drug, from three to ten parts by weight of saccharin or its alkali metal salts to each part by weight of cylamate sodium or cyclamate calcium, wherein the saccharin is present in an amount not less than one percent by weight.

Although it has been common practice to utilize sucrose and other sweetening agents to modify the taste of bitter drugs, it has been believed impossible prior to the present invention to utilize sufficient amounts of these materials to neutralize the bitter taste of many of the best-known and most effective drugs. Although it has long been recognized that artificial sweetening agents such as saccharin are many times as sweet as sucrose, it was thought that, in high concentrations, saccharin

possesses a taste which is "so sweet that it is bitter" [Fischelis, Principles of Pharmacy, 4th Edition, W. B. Saunders Company (1937) at page 798]. Similar observations have been made in relation to cyclamates. The following statement is taken from page 560 of Volume XIII of the Encyclopedia of Chemical Technology, the Interscience Encyclopedia, Inc., New York, 1954:

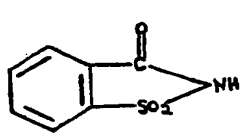
> "Both saccharin and cyclamate in excessive concentrations tend to display a bitter note to the taste. The exact concentration at which this effect occurs varies with the individual. With saccharin the threshold occurs in the vicinity of 0.1%. In the case of cyclamate, the bitter note may be encountered by most individuals at a concentration of approximately 0.8%. These concentrations in both instances are well above the level of ordinary use."

Therefore, the use of saccharin prior to the present invention has been limited to comparatively low concentrations of from 0.01 to 0.1 percent. Saccharin has been used primarily as a substitute for sugar in situations where a substitute was deemed desirable for economic or nutritional purposes.

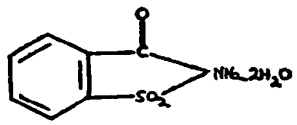
It has now been found that saccharin can be used in high concentrations of from about one to ten percent by weight in combination with lesser concentrations and proportions of cyclamate, to provide sweetening compositions and especially to mask the taste of bitter drugs in oral fluid preparations. The amount of saccharin used is dependent on the taste intensity of the bitter drug and generally takes from one to twenty parts of saccharin to each part of bitter drug. The amount of cyclamate used depends upon the amount of saccharin used. It may vary from about one-third to about one-tenth the amount of the saccharin, the proportion being fitted to the requirements of the specific composition.

The present invention also embodies a sweetening composition comprising from three to ten parts by weight of the saccharin component to each part by weight of the cyclamate component, wherein saccharin is present in an amount not less than one percent by weight. Such a sweetening agent can be dry or fluid in form and should be suitable for direct incorporation into foods, beverages or pharmaceuticals, to provide high concentrations of saccharin, i.e., one percent by weight or above.

Saccharin is an artificial sweetening agent which, as indicated above, is several hundred times as sweet as sucrose. The variation in sweetening power is the result of the wide variation in sensory responses of individual persons. It is so sweet that many people can taste it in a concentration of one part in 70,000 parts of water. It can be prepared both as saccharin itself and as various salts of saccharin, principally the alkali metal salts. The ammonium salt is meant to be included in this group as it is often times classified as an alkali metal salt. The sodium salt is often referred to as soluble saccharin.



Saccharin

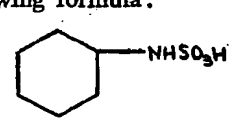


Sodium or Soluble Saccharin

The ammonium salt is unusual in that it is 700 times as sweet as saccharin by some tests. One gram of saccharin is soluble in 300 milliliters of water at 25 degrees centigrade. One gram of saccharin is soluble in 25 milliliters of boiling water, thirty milliliters of alcohol and fifty milliliters of glycerol. Sodium or soluble saccharin, on the other hand, is soluble at the rate of 83 grams in 100 milliliters of water. Two grams of sodium saccharin are soluble in 100 milliliters of alcohol. It is obvious, therefore, that saccharin, if it is to be used in high concentrations, is useful in alcoholic fluid preparations, i.e., elixirs. Alkali metal salts of saccharin, on the other hand are more soluble in aqueous preparations and would be more advantageously used therein if it is to be used in high concentrations.

The safety of the use of high concentrations of saccharin has been definitely established by scientists of the Food and Drug Administration as reported by Lehman, Assoc. Food Drug Officials (U.S.). Quarterly Bull. 14, 82 (1950). It was there reported that saccharin produced no apparent effects at high levels of feeding and consequently is considered safe for food additives.

Cyclamate is a synthetic sweetening agent of the following formula:



Sweetness is apparent at a dilution of one part in 10,000 parts of water. It can be prepared

both as the free acid and as various salts such as the alkali metal salts and the alkaline earth metal salts. The sodium and calcium salts are freely soluble in water and are preferred for the composition of this invention. Both salts have been recognized as safe additives for food, drugs, beverages, and the like.

Although it is operable in both the liquid and solid preparations of the invention to use saccharin in the concentration of from one to ten percent by weight, it is preferred to use from about two to six percent. It is operable to use cyclamate sodium or cyclamate calcium in an amount equal to from one-third to one-tenth of the amount of saccharin used but from about one-fourth to one-eighth is preferred. The compositions of the invention can be used with such intensely bitter drugs as barbiturates, alkaloids and antibiotics. Masking the taste of therapeutic amounts of these materials in fluid preparations has been noted for lack of success. The usual procedure is to use sugar, but this has been of little avail. Other flavors are of small help. Elixir of phenobarbital, for example, is widely used and is an excellent example of the usual inability to solve the bitter taste problem. Other materials possessing a bitter taste which can be improved by the present invention are penicillin salts, especially sodium or potassium penicillin G, amine salts, codeine salts, sulfamethazine, erythromycin, quinine salts, ephedrine salts, and beta-(orthomethoxyphenyl)-isopropyl-methylamine. By the use of a high concentration of saccharin and a lower concentration of cyclamate sodium or cyclamate calcium in accordance with the present invention, the bitter taste of these materials has been successfully neutralized. Further improvements are of course possible by the usual balancing of other flavor and solvent factors, such as by the addition of sucrose, glycerin U.S.P. and especially propylene glycol. Further improvement is noted by the use of sodium carboxymethylcellulose.

In general, the sweetening composition can be prepared by simple association of the saccharin and cyclamate in the proportions and concentrations indicated. The usual diluents and carriers can also be included where there is no incompatability with the sweeteners or the intended use.

Various forms of the composition of the invention find uses in harmony with the requirements of a particular industry or individual. Solid preparations such as tablets, pills, powders, or the like can be prepared. Liquid preparations can also be prepared, preferably using a fluid in which both the saccharin and cyclamate are soluble.

The following examples are illustrative of the composition of this invention and are not to be construed as limiting. All percentages by weight unless otherwise indicated.

Example 1

Pediatric Cough Formulas

A typical cough formula which has a greatly reduced bitter taste by application of the present invention contains the following ingredients for each cubic centimeter:

Propylene glycol U.S.P.	25% v/v
Phenobarbital U.S.P.	8 mg.
Glycerin U.S.P.	40% v/v
Sodium carboxymethylcellulose low viscosity	10 mg.
Beta - (orthomethoxyphenyl)-isopropyl-methylamine	4 mg.
Codeine phosphate U.S.P.	2 mg.
Sodium citrate U.S.P.	60 mg.
Saccharin Sodium U.S.P.	40 mg.
Cyclamate Sodium	5 mg.
Aromatic Flavor	0.2 mg,
Deionized water	Sufficient to make up one c.c

Another typical such formulation contains the following ingredients per cubic centimeter:

Propylene glycol U.S.P.	12% v/v
Phenobarbital U.S.P.	4 mg.
Glycerin U.S.P.	40% v/v
Sodium carboxymethylcellulose low viscosity	10 mg.
Beta - (orthomethoxyphenyl)-isopropyl-methylamine	4 mg.
Codeine phosphate U.S.P.	4 mg.
Sodium citrate U.S.P.	60 mg.
Saccharin Sodium U.S.P.	30 mg.
Cyclamate Sodium	5 mg.
Aromatic Flavour	0.25 mg.
Deionized water	Sufficient to make up one c.c

One thousand cubic centimeters of the above formulations are prepared by multiplying the amounts of the ingredients shown by one thousand. The formulations are prepared by heating the propylene glycol to dissolve the phenobarbital, stirring constantly. The solution is removed from the heat and glycerin U.S.P. and carboxymethylcellulose are added. The whole is stirred. The remaining ingredients are dissolved in about thirty percent volume/volume of deionized water. The two preparations are mixed and stirred for four hours and then strained. The dose for a one year old child of such a preparation is one cubic centimeter.

Example 2

Ulcer Remedy

The following formula is an example using high saccharin with propylene glycol to cover the bitter taste of phenobarbital and scopolamine methyl bromide. Methylparaben is employed in the composition as a preservative and fungistatic agent.

Sodium Carboxymethylcellulose low viscosity	1%
Glycerin	20%
Propylene glycol	30%
Alcohol	20%
Phenobarbital	2%
Scopolamine methyl bromide	0.05%
Saccharin Sodium U.S.P.	2.0%
Cyclamate Sodium	0.5%
Methylparaben (Methyl-*p*-hydroxybenzoate)	0.1%
Colour	0.002%
Water	Sufficient to make up 100%

EXAMPLE 3

Penicillin Preparation

For each 100 cubic centimeters the following ingredients are intermixed using conventional pharmaceutical techniques:

Saccharin Sodium	10 grams
Potassium Penicillin G	14 grams
Glycine	20 grams
Cyclamate Calcium	3 grams
Imitation Oil of Grenadine	0.05 cc.
Imitation Chocolate	0.3 cc.
Deionized water	Sufficient to make up 100 cc.

Water is added prior to use. The bitter taste of the penicillin salt is greatly reduced.

EXAMPLE 4

Phenobarbital Solution

The following formulation is prepared using conventional procedures to cover the taste of phenobarbital:

Sodium carboxymethylcellulose low viscosity	1%
Propylene glycol	50%
Alcohol	20%
Phenobarbital	2%
Saccharin Sodium U.S.P.	1%
Methylparaben (Methyl-*p*-hydroxybenzoate)	0.1%
Cyclamate Sodium	0.2%
Aromatic Flavouring Oils	0.1%
Color	0.002%
Water	to 100%

EXAMPLE 5

Compressed Tablets of Saccharin-Cyclamate

Compressed tablets are prepared containing in each tablet:

Saccharin	30 mg.
Cyclamate Calcium (calcium cyclohexyl-sulfamate)	3.5 mg.
Polyethylene glycol (molecular weight 6000)	52 mg.
Sodium benzoate	4.5 mg.

All the finely powdered ingredients, except the sodium benzoate, are mixed intimately and granulated with a two percent aqueous solution of methylcellulose (low viscosity). After drying thoroughly, the granules are mixed with the sodium benzoate and compressed into tablets. On use in hot beverages, the tablets dissolved rapidly and produced a satisfactory sweetness without undesirable after-taste.

In the above formulation the saccharin can be replaced by saccharin sodium to enable faster solution in hot or cold liquids.

EXAMPLE 6

Effervescent Tablets of Saccharin-Cyclamate

Effervescent tablets are prepared containing in each tablet:

Saccharin Sodium	60 mg.
Cyclamate Sodium	12 mg.
Sodium bicarbonate	80 mg.
Tartaric acid	7.5 mg.
Citric acid	35 mg.
Sodium benzoate	4.5 mg.

All the finely powdered materials, except the sodium benzoate, are mixed intimately and granulated like an effervescent salt by heating in a steam jacketed pan to release the water of crystallization of the citric acid. As soon as all the fine particles mass together, the material is screened and dried thoroughly. Before compressing into tablets the granules are lubricated well with the finely powdered sodium benzoate. On use in cold or hot liquids, the tablets disintegrate rapidly producing satisfactory sweetness without undesirable after-taste.

EXAMPLE 7

Drops Saccharin-Cyclamate

A solution is prepared containing in each cubic centimeter:

Saccharin Sodium	105 mg.
Cylamate Sodium	14 mg.
Deionized water q.s.	1 ml.

This is dispensed in a special dropper bottle so that two drops contain fifteen milligrams of saccharin sodium and two milligrams of cyclamate sodium. This preparation produces satisfactory sweetness without undesirable after-taste.

EXAMPLE 8

Codeine Solution

Using any of the known oral codeine phosphate high-alcoholic elixirs, the bitter taste of codeine phosphate can be greatly reduced by the addition of 1.5 percent saccharin and 0.5 percent cyclamate sodium.

EXAMPLE 9

Sulpha Suspension

Using any of the known oral triple sulphonamide suspensions containing sulphamethazine, sulphadiazine, and sulphamerazine, the bitter taste of the sulphamethazine can be disguised by the use of six percent ammonium saccharin and 0.66 percent cyclamate calcium.

Similarly, the bitter taste of preparations

containing beta-(orthomethoxyphenyl) - isopropyl - methylamine, atropine sulfate, and hyoscyamine hydrobromide can be greatly reduced by the addition of saccharin and cyclamate calcium.

Preparations containing bitter drugs which must be chewed before swallowing (and which therefore remain in the oral cavity for a considerable length of time) will also benefit by the addition of high concentrations of saccharin and a low concentration of cyclamate in accordance with the present invention.

We are aware of the provisions of the Public Health (Preservatives etc. in Food) Regulations 1925-53 and in so far as our invention relates to the manufacture for sale in the United Kingdom and/or sale in the United Kingdom of sweetening compositions for addition to foodstuffs etc., we make no claim to use the invention in contravention of the law.

WHAT WE CLAIM IS:—

1. A sweetening composition comprising from three to ten parts by weight of saccharin or its alkali metal salts to each part by weight of cyclamate sodium and/or cyclamate calcium, wherein saccharin or the saccharin salt is present in an amount not less than one percent by weight.

2. The sweetening composition of claim 1 in compressed tablet form comprising the sweetening agents and compressed tablet adjuvants.

3. The sweetening composition of claim 1 in effervescent tablet form comprising the sweetening agents and effervescent tablet adjuvants.

4. A fluid sweetening composition comprising from three to ten parts by weight of saccharin or its alkali metal salts to each part by weight of cyclamate sodium and/or cyclamate calcium, wherein saccharin is present in an amount not less than one percent by weight in association with a liquid diluent.

5. An oral pharmaceutical composition comprising a bitter tasting drug, from three to ten parts by weight of saccharin or its alkali metal salts to each part by weight of cyclamate sodium and/or cyclamate calcium, wherein saccharin is present in an amount not less than one percent by weight.

6. An oral fluid pharmaceutical preparation as claimed in claim 5, wherein saccharin or its salt is present in an amount from one to ten percent by weight.

7. An oral fluid pharmaceutical preparation as claimed in claim 5, wherein saccharin or its salt is present in an amount from about two to about six percent by weight.

8. An oral fluid pharmaceutical preparation as claimed in any of claims 5 to 7, in which the bitter tasting drug is beta-(orthomethoxyphenyl)-isopropyl-methylamine, phenobarbital, a bitter penicillin salt, a soluble codeine salt or sulphamethazine.

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